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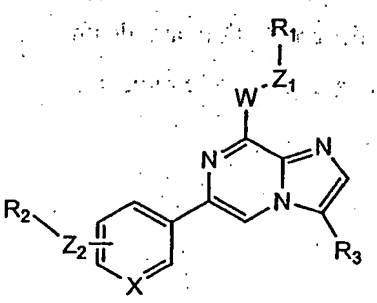
(54) Title: CERTAIN 8-HETEROARYL-6-PHENYL-IMIDAZO[1,2-A]PYRAZINES AS MODULATORS OF KINASE ACTIVITY



(I)

(57) Abstract: This invention pertains to compounds of Formula I: (I) and all pharmaceutically-acceptable forms thereof. The variables R_1, R_2, R_3, Z_1, Z_2, W, and X shown in Formula I are defined herein. The invention also provides pharmaceutical compositions containing one or more compound of Formula I, or a pharmaceutically acceptable form of such compounds, and one or more pharmaceutically acceptable carriers, excipients, or diluents. The invention further comprises methods of treating patients suffering from certain diseases and disorders responsive to EphB4 kinase modulation, which comprise administering to such patients an amount of a compound of Formula I effective to reduce signs or symptoms of the disease or disorder. These diseases include cancer, including of breast neoplasma, endometrial cancer, colon cancer, and neck squamous cell carcinoma. Thus methods of treatment include administering a sufficient amount of a compound or salt of the invention to decrease the symptoms or slow the progression of these diseases or disorders. The invention also encompasses methods of treating other animals, including livestock and domesticated companion animals, suffering from a disease or disorder responsive to EphB4 modulation. Methods of treatment include administering a compound of Formula I as a single active agent or administering a compound of Formula I in combination with one or more other therapeutic agent. The invention also includes a method for determining the presence of $EphB_4$ kinase in a sample, comprising contacting the sample with a compound of Formula I, or form thereof, and detecting the amount of compound or form bound to $EphB_4$ kinase, and therefrom determining the presence or absence of $EphB_4$ kinase in the sample.

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inflammatory diseases. The multifaceted role of kinases in key cell signaling pathways provides a significant opportunity to identify novel drugs targeting kinases and signaling pathways. Diseases mediated by receptor kinase activity include, but are not limited to, diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion, and angiogenesis associated with tumor growth.

[0003] The recently demonstrated efficacy of multiple kinase inhibitors in the treatment of cancer, including the FDA approval of the kinase inhibitor GLEEVEC (imatinib mesylate), a c-Kit, PDGFR, and Abl kinase inhibitor, for the treatment of chronic myeloid leukemia, and the proof of clinical efficacy for AVASTIN, a VEGF modulator that inhibits angiogenesis, is testimony to the great clinical potential of kinase and other signal transduction inhibitors as therapeutics.

[0004] Kinases also play a key role in angiogenesis. Angiogenesis, the formation of new blood vessels from preexisting ones, plays a critical role in many pathological settings, including cancer, chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis, and macular degeneration. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization.

[0005] Angiogenesis is regulated by multiple cell-signaling pathways, including pathways controlled by cellular kinases. Blocking angiogenesis, through the modulation of cell kinases, therefore, represents an effective approach to the treatment of diseases such as cancer.

[0006] The process of angiogenesis is complex, requiring the concerted actions of multiple angiogenic mediators as well as the participation of different cell types. Key angiogenesis mediators, including, VEGF, FGF, and angiopoietin 1 and 2 (Ang1 and Ang2) that bind to their cognate receptors (VEGFRs, FGFRs and Tie1 and Tie2, respectively) expressed on endothelial cells, as well as platelet-derived growth factor (PDGF) that binds to its receptor (PDGFRs) expressed on pericytes and smooth muscle cells have been identified. Recent studies indicate that several members of the ephrin family and their receptor Eph family are novel regulators of angiogenesis.

in mitosis. Hsp90 substrates include a number of steroid hormone receptors including the androgen receptor (AR), estrogen receptor, and glucocorticoid receptor.

[0013] Hsp90 has been specifically implicated in the proper folding of a number of tyrosine and threonine kinases. It also insures the correct folding and activity of numerous kinases involved in cell proliferation and differentiation, many of which also play roles in oncogenesis.

[0014] Hsp90 can also function as part of a multi-component complex interacting with many other co-chaperone proteins. While Hsp90 forms a multi-component complex to some extent in normal cells, nearly all Hsp90 present in cultured tumor cells has been shown to be part of a multi-component complex. A number of known oncogenic proteins that are Hsp90 substrate proteins, depend on the chaperone activity of the Hsp90 complex for correct folding. Thus Hsp90 functions as a supplier of oncogenic proteins in tumor cells. Hsp90 complex in tumor cells also exhibits higher ATPase activity than Hsp90 from non-cancerous cell lines.

Geldanamycin, a natural product, is an Hsp 90 inhibitor that binds to the ATP binding site of Hsp90 inhibiting ATP hydrolysis but not substrate protein binding. Substrate proteins that reside longer on Hsp90 when ATP hydrolysis is inhibited are ubiquinated, and subsequently degraded. Disrupting the function of the Hsp90 complex has been shown to deplete oncogenic kinases (via ubiquitin-mediated proteasomal degradation) and decrease tumor growth. The Hsp90 complex present in tumor cells exhibits much higher affinity for geldanamycin and for 17-AAG, a geldanamycin derivative, than Hsp90 in non-tumor cells. Thus inhibitors of the Hsp90 complex have the ability to convert this protein from a chaperone that insures correct protein folding of oncogenic proteins to a selective protein degradation tool.

[0015] Because of its roles in cell cycle control, cell growth, and oncogenesis the Hsp90 complex is an important target for anti-cancer therapeutics. The ability of certain Hsp90 complex inhibitors to cause this protein complex to selectively target its substrate proteins for degradation makes the Hsp90 complex an especially desirable anti-cancer target. Hsp90 is also a potential drug target for autoimmune and degenerative disease because of its role in modulating the cellular stress response.

wherein R_4 and R_5 are independently hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, or halogen; and m is 0, 1, or 2.

R_6 and R_7 are independently (i) hydrogen or C_1-C_6alkyl or (ii) phenyl or heteroaryl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and $-C(O)R_{13}$.

W is phenyl or a 5- or 6-membered heteroaryl containing from 1 to 4 heteroatoms independently chosen from nitrogen, oxygen, and sulfur; wherein W is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl.

X is N or CH.

R_2 is C_1-C_7alkyl, C_3-C_7cycloalkyl(C_0-C_2alkyl), heterocycloalkyl(C_0-C_2alkyl), C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, or (C_1-C_6alkoxy)C_1-C_6alkoxy; or

R_2 is phenyl(C_0-C_2alkyl) or heteroaryl(C_0-C_2alkyl), each of which is substituted with 0 to 3 substituents independently chosen from (iii) hydroxy, halogen, nitro, cyano, amino, sulfonamide, -CHO, C_1-C_6haloalkyl, and C_1-C_6haloalkoxy,and (iv) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, heterocycloalkyl(C_0-C_2alkyl), and $-C(O)R_{13}$; each of which (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C_1-C_4alkoxy, C_3-C_7cycloalkyl, and mono- and di-(C_1-C_4alkyl)amino.

Z_2 is

For example certain compounds described herein inhibit $EphB_4$, Tie-2, c-Kit, and VEGF-R2 kinases. Certain compounds described herein inhibit $EphB_4$, exhibiting an IC_{50} of 1 micromolar or less in the assay of Example 7 and also exhibit an IC_{50} of 1 micromolar or less for the inhibition of Tie-2, c-Kit, and VEGF-R2 in the biochemical assay of Example 9.

[0020] The invention includes a pharmaceutical composition, comprising one or more compounds Formula I or any pharmaceutically acceptable form thereof, together with at least one pharmaceutically acceptable carrier or excipient.

[0021] The invention also pertains to packaged pharmaceutical compositions which comprise a pharmaceutical composition, comprising one or more compounds Formula I or any pharmaceutically acceptable form thereof, together with at least one pharmaceutically acceptable carrier or excipient in a container and with instructions for using the pharmaceutical composition to treat a patient suffering from a disease or disorder responsive to kinase modulation and/ or Hsp90 complex modulation. The invention further pertains to a method for modulating kinase activity, preferably for modulating the activity of multiple oncogenic and/ or angiogenic kinases, such as $EphB_4$, Tie-2, c-Kit, and VEGF-R2. In certain embodiments the invention includes inhibiting the binding of the natural ligand of a kinase, particularly a natural ligand of $EphB_4$, Tie-2, c-Kit, or VEGF-R2, the method comprising contacting a cell or cells expressing the kinase, such as $EphB_4$ kinase with a compound according to Formula I or form thereof in an amount sufficient to detectably decrease the level $EphB_4$ kinase activity *in vitro*.

[0022] Furthermore the invention includes a method for treating a patient having a disease or disorder responsive to kinase modulation and/ or Hsp90 complex modulation, comprising administering to the patient and effective amount of a compound or form thereof according to Formula I. The invention includes methods of treatment in which the patient is a human patient, and in which the patient is a companion animal, such as a cat or dog, and in which the patient is a livestock animal, such as a horse, cow, or pig. The invention particularly includes methods in which the disease or disorder responsive to kinase modulation is cancer or a condition characterized by pathological angiogenesis.

[0026] Certain terms to be used herein are provided prior to setting forth the invention in detail. Compounds of the present invention are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0027] Formula I includes all subformulae thereof. For example Formula I includes compounds of Formulas 1 to 9. "A compound of Formula I" includes compounds of Formula I, as well as pharmaceutically acceptable salts, solvates and prodrugs of any compound of Formula I.

[0028] Certain compounds are described herein using a general formula that includes variables, e.g. R_1, R_2, R_3, W, X, Z_1, and Z_2. Unless otherwise specified, each variable within such a formula is defined independently of other variables.

[0029] In accordance with the usual meaning of "a" and "the" in patents, reference to "a" kinase or "the" kinase is inclusive of one or more kinases. Unless otherwise specified the term "compounds" includes all pharmaceutically acceptable forms of the disclosed structures.

[0030] In certain situations, the compounds of Formula I may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present invention. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as

from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those having one or more sulfonyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; aminoalkyl groups including groups having one or more N atoms and from 1 to about 8, or from 1 to about 6 carbon atoms; aryl having 6 or more carbons and one or more rings, (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O, or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen or amino.

[0035] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CHO is attached through carbon of the carbonyl (C=O) group.

[0036] As used herein, "alkyl" includes both branched and straight chain saturated aliphatic hydrocarbon groups, having the specified number of carbon atoms, generally from 1 to about 12 carbon atoms. The term C_1-C_7alkyl as used herein indicates an alkyl group having from 1 to about 7 carbon atoms. When C_0-$C_n$alkyl is used herein in conjunction with another group, for example, heterocycloalkyl(C_0-C_2alkyl), the indicated group, in this case heterocycloalkyl, is either directly bound by a single covalent bond (C_0), or attached by an alkyl chain having the specified number of carbon atoms, in this case from 1 to about 2 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, 3-methylbutyl, t-butyl, n-pentyl, and sec-pentyl. Alkyl groups described herein typically have from 1 to about 12 carbons atoms. Preferred alkyl groups are lower

to about 4 carbon atoms and further attached to the core molecule through an oxygen bridge.

[0042] "Alkanoyl" indicates an alkyl group as defined above, attached through a keto (-(C=O)-) bridge. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2alkanoyl group is an acetyl group having the formula $CH_3(C=O)$-.

[0043] As used herein, "alkylthio" means alkyl-S-, where the alkyl group is an alkyl group as defined above having the defined number of carbon atoms. An exemplary alkylthio group is methylthio.

[0044] As used herein the term "alkoxycarbonyl" indicates an alkoxy group, as defined above, having the indicated number of carbon atoms, attached through a keto (-(C=O)-) bridge. The alkoxy moiety of the alkoxycarbonyl group has the indicated number of carbon atoms. The carbon of the keto bridge is not included in this number. C_3alkoxycarbonyl indicates for example, groups of the formula $CH_3(CH_2)_2$-O-(C=O)- or $(CH_3)_2(CH)$-O-(C=O)-.

[0045] As used herein "amino(alkyl)" is an alkyl group as defined herein, having the indicated number of carbon atoms, and substituted with at least one amino substituent ($-NH_2$). When indicated aminoalkyl groups, like other groups described herein, may be additionally substituted.

[0046] As used herein, the term "mono- and/ or di-(alkyl)amino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. The alkyl groups are independently chosen. Examples of mono- and/ or di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino. "Mono- and/or dialkylaminoalkyl" groups are mono- and/ or di-alkylamino groups attached through an alkyl linker having the specified number of carbon atoms, for example a di-methylaminoethyl group. Tertiary amino substituents may by designated by nomenclature of the form *N*-R-*N*-R', indicating that the groups R and R' are both attached to a single nitrogen atom.

[0052] "Haloalkoxy" indicates a haloalkyl group as defined above attached through an oxygen bridge.

[0053] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, or iodo.

[0054] As used herein, "heteroaryl" indicates a stable 5- to 7-membered monocyclic aromatic ring which contains from 1 to 4, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5 to 7 membered aromatic ring which contains from 1 to 4, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl.

[0055] The term "heterocycloalkyl" indicates a saturated monocyclic group containing from 1 to about 3 heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a saturated bicyclic ring system having at least one N, O, or S ring atom with remaining atoms being carbon. Monocyclic heterocycloalkyl groups have from 4 to about 8 ring atoms, and more typically have from 5 to 7 ring atoms. Bicyclic heterocycloalkyl groups typically have from about five to about 12 ring atoms. The size of a heterocycloalkyl groups is given by the number of ring carbon atoms the group contains. For example, a C_2-C_7heterocycloalkyl group contains from 2 to about 7 ring carbon atoms with the remaining ring atoms, up to about 3 per ring, being chosen from N, O, and S. Preferred heterocycloalkyl groups include C_3-C_6 monocyclic heterocycloalkyl groups that contain from 5 to 7 ring atoms and 1 or 2 heteroatoms independently chosen from N, O, and S. Examples of

Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

[0060] The term "prodrugs" includes any compounds that become compounds of Formula I when administered to a mammalian subject, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I.

[0061] The term "active agent" is used to indicate a compound, including any pharmaceutically form thereof, or natural product, which has biological activity. Preferably an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

[0062] "Angiogenic kinases" include but are not limited to $EphB_4$, VEGF-R2, and Tie-2.

[0063] "Oncogenic kinases" include but are not limited to c-Kit and PDGFR-alpha.

[0064] "Diseases or disorders responsive to kinase modulation" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including cell proliferation, differentiation, and invasion. Diseases responsive to kinase modulation include but are not limited to tumor growth, pathological angiogenesis supporting solid tumor growth, and diseases characterized by excessive local vascularization such as diabetic retinophathy and macular degeneration, and inflammation.

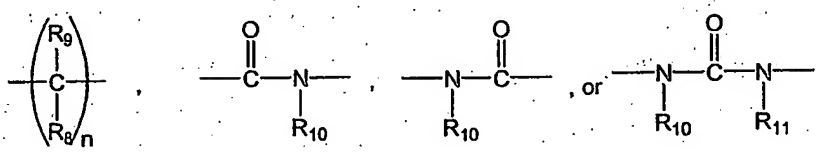
[0065] The term "effective amount" of a compound of this invention means an amount effective, when administered to a human or non- human patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to

CHO, halogen, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl.

X is N or CH.

R_2 is C_1-C_7alkyl, C_3-C_7cycloalkyl(C_0-C_2alkyl), heterocycloalkyl(C_0-C_2alkyl), C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, or (C_1-C_6alkoxy)C_1-C_6alkoxy; or R_2 is phenyl(C_0-C_2alkyl) or 5- or 6-membered heteroaryl(C_0-C_2alkyl), each of which is substituted with 0 to 3 substituents independently chosen from (i) hydroxy, halogen, nitro, cyano, amino, sulfonamide, -CHO, C_1-C_6haloalkyl, and C_1-C_6haloalkoxy, and (ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and heterocycloalkyl(C_0-C_2alkyl); each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C_1-C_4alkoxy, C_3-C_7cycloalkyl, and mono- and di-(C_1-C_4alkyl)amino.

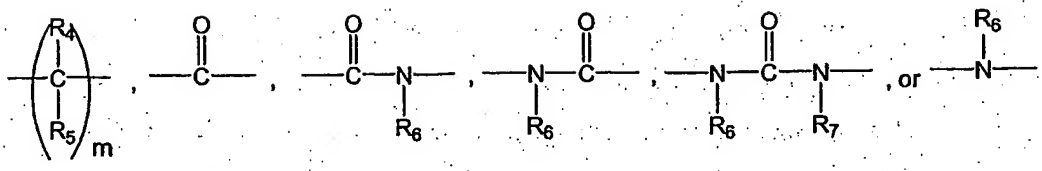
Z_2 is



wherein R_8 and R_9 are independently hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, or halogen; and n is 0, 1, or 2.

R_{10} and R_{11} are independently (iii) hydrogen or C_1-C_6alkyl; or (iv) phenyl or a 5- or 6 membered heteroaryl ring, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl.

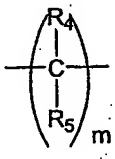
R_3 is hydrogen or C_1-C_6alkyl, or R_3 is C_3-C_7cycloalkyl(C_0-C_2alkyl), heterocycloalkyl(C_0-C_2alkyl), phenyl, or a 5- or 6-membered heteroaryl, each of



wherein R_4 and R_5 are independently hydrogen or C_1-C_6alkyl, and m is 0, 1, or 2; and R_6 and R_7 are independently hydrogen, C_1-C_6alkyl, or phenyl.

[0071] Other embodiments of the invention include compounds and salts of Formula 1 and Formula 1-A in which

Z_1 is



wherein R_4 and R_5 are independently hydrogen, methyl, or ethyl; and m is 0 or 1. In some preferred embodiments m is 0.

The W Variable

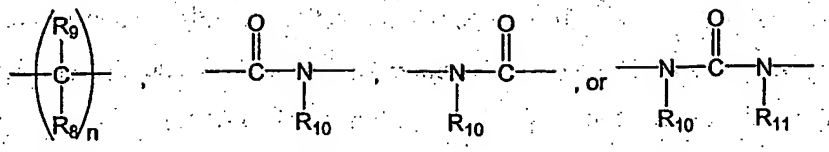
[0072] The invention includes compounds and salts of Formula 1 and Formula 1-A in which:

[0073] W is phenyl, pyridyl, pyrimidinyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl.

[0074] The invention also includes compounds and salts of Formula 1 and Formula 1-A in which:

W is phenyl, pyridyl, pyrimidinyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, and mono- and di-(C_1-C_4alkyl)amino.

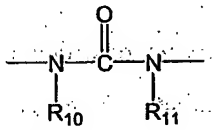
Z_2 is



wherein R_8 and R_9 are independently hydrogen or C_1-C_6alkyl; and n is 0, 1, or 2; and R_{10} and R_{11} are independently hydrogen, C_1-C_6alkyl, or phenyl.

[0080] The invention includes compounds and salts of Formula 1 and Formula 1-A in which:

Z_2 is



wherein, R_{10} and R_{11} are independently hydrogen, methyl, or ethyl.

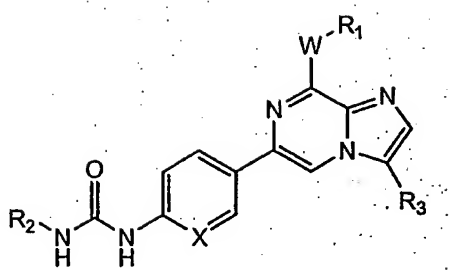
[0081] In certain embodiments R_{10} and R_{11} are both hydrogen.

The R_2 Variable

[0082] The invention includes compounds and salts of Formula 1 and Formula 1-A in which:

R_2 is phenyl, pyridyl, pyrimidinyl, pyrazinyl, imidazolyl, pyrrolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which may be either directly attached or bound via a C_1-C_2alkyl linker, and each of which is substituted with 0 to 3 substituents independently chosen from: (i) hydroxy, halogen, nitro, cyano, amino, sulfonamide, -CHO, C_1-C_6haloalkyl, and C_1-C_6haloalkoxy, and (ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and heterocycloalkyl(C_0-C_2alkyl); each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C_1-C_4alkoxy, C_3-C_7cycloalkyl, and mono- and di-(C_1-C_4alkyl)amino.

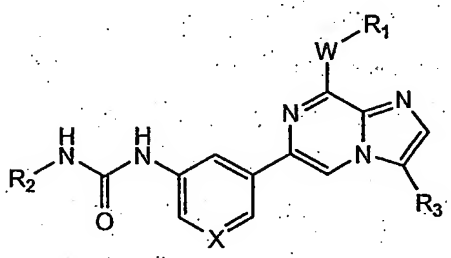
[0083] In other embodiments the invention includes compounds of Formula 1 and Formula 1-A, and forms thereof, in which:



(Formula 5)

in which R_1, R_2, R_3, X, and W may carry any of the definitions set forth above for these variables.

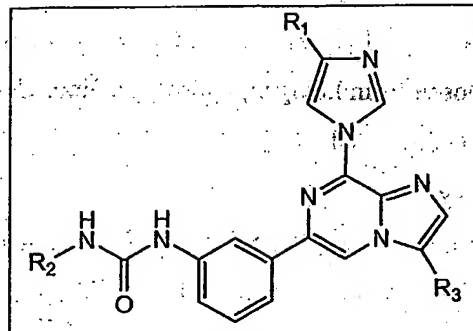
[0088] The invention further pertains to compounds of Formula 6 and forms thereof



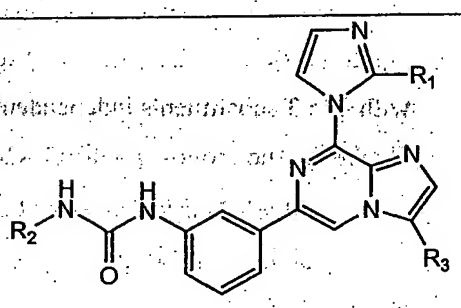
(Formula 6)

in which R_1, R_2, R_3, X, and W may carry any of the definitions set forth above for these variables.

[0089] The invention pertains to compounds of Formula 7 to 9 and forms thereof:



(Formula 7)



(Formula 8)

[0097] Modulation of kinase activity is determined by a biochemical assay such as the $EphB_4$ FRET assay of Example 7, or the c-Kit, TIE-2, and VEGF-R2 biochemical FRET assays of Example 9.

[0098] Inhibition of Hsp90 complex activity results in reduced cell proliferation. Thus, modulation of Hsp90 complex activity is determined by a cell proliferation assay such as the tumor cell proliferation assay of Example 11. Hsp90 complex activity inhibition may also be observed via Western blot, for example by the Western blot protocol of Example 10. In this protocol reduced level of Hsp90 substrate proteins, such as ErbB2, Akt, or Raf indicates inhibition of Hsp90 complex activity.

[0099] The invention includes compounds of Formula I and forms thereof, which exhibit an IC_{50} of 10 micromolar or less, more preferably 500 nanomolar or less, and more preferably 100 nanomolar or less, in a standard *in vitro* assay of $EphB_4$ kinase activity (such as the assay of Example 7). The invention also includes compounds of Formula I and forms thereof, which exhibit IC_{50} values of 2 micromolar or less in each of the c-Kit, Tie-2, and VEGF-R2 biochemical assays described in Example 9.

[0100] The invention includes a method of modulating kinase activity. For example the invention includes a method of inhibiting angiogenic kinase activity, the method comprising contacting a cell or cells expressing angiogenic kinase with a compound of Formula I or any pharmaceutically acceptable form thereof in an amount sufficient to detectably decrease activity of the angiogenic kinase *in vitro*. The invention includes a method of modulating binding of ATP to the Hsp90 complex, the method comprising contacting a cell or cells expressing Hsp90 complex with a compound of Formula I or any pharmaceutically acceptable form thereof according in an amount sufficient to detectably decrease the level of an Hsp90 complex substrate protein *in vitro*. Decreased level of Hsp90 complex substrate protein may be observed via Western blot, for example by the Western blot protocol of Example 10. The substrate may be ErbB2, Akt, or Raf or other Hsp90 complex substrate.

[0105] Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0106] Effective concentrations of one or more of the compounds of the invention including pharmaceutically acceptable salts, esters or other derivatives thereof are mixed with a suitable pharmaceutical carrier, excipients, adjuvant, or vehicle. In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts of the compounds or prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0107] Upon mixing or addition of the compound(s) of the invention, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the chosen carrier or vehicle. The effective concentration sufficient for ameliorating the symptoms of the disease, disorder, or condition treated and may be empirically determined.

[0108] Compounds of general the invention may be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations.

[0109] Dosage formulations suitable for oral use, include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. Oral formulations contain between 0.1 and 99% of a compound of the

[0114] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol substitute, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan substitute. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n- propyl p-hydroxybenzoate.

[0115] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Emulsions

[0116] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

Dispersible powders

[0121] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables.

[0122] Compounds of the invention may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrathecal injection or infusion techniques. The compound or compounds of the invention, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. In many compositions for parenteral administration the carrier comprises at least about 90% by weight of the total composition. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil.

Suppositories

[0123] Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Topical formulations

collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

[0129] Compounds of the invention may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Other formulations

[0130] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol, and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0131] Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

Additional components

[0132] The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance antimicrobial effects of compounds of the present invention. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

[0133] Pharmaceutical compositions of the invention may also contain additional active agents can be chosen from a wide variety of molecules, which can function in different ways to enhance the therapeutic effects of a compound of the

Formula I with multiple kinases, especially with c-Kit, VEGF-R2, $EphB_4$, and Tie-2, results in the pharmaceutical utility of these preferred compounds.

[0139] Accordingly, the invention includes a method of treating a mammal, preferably a human, having a disease or disorder responsive to kinase or Hsp90 complex modulation, comprising administrating to the mammal an effective amount of a compound of Formula I.

[0140] Methods of treatment also include modulating kinase and/or Hsp90 complex activity, by inhibiting ATP binding or hydrolysis by a kinase or the Hsp90 complex or by some other mechanism, *in vivo*, in a patient suffering from a disease or disorder responsive to kinase or Hsp90 complex modulation, by administering a sufficient concentration of a compound of Formula I to inhibit kinase and/ or Hsp90 complex activity *in vitro*. By "sufficient concentration" of a compound administered to the patient is meant the concentration of the compound available in the patient's system to combat the disease or disorder. Such a concentration may be ascertained experimentally, for example by assaying blood concentration of the compound, or theoretically, by calculating bioavailability.

[0141] In a preferred embodiment, the condition responsive to kinase modulation and/ or Hsp90 complex modulation is cancer or pathological angiogenesis.

[0142] The invention includes a method of treating a patient having cancer or pathological angiogenesis by administering a compound of Formula I. The invention provides methods of treatment in which a compound of the invention is the only active agent given to a patient and also includes methods of treatment in which a compound of Formula I is given to a patient with an additional active agent.

Diseases and disorders responsive to kinase modulation

[0143] Certain compounds described herein are useful for treating a patient suffering from a disease or disorder responsive to kinase modulation.

[0144] Protein kinases, the largest family of human enzymes, are now considered to be the largest druggable target class. Encompassing well over 500 proteins (2% of the human genome), kinases play critical roles in signaling pathways controlling fundamental cellular processes such as proliferation, differentiation, and

cell lung cancer, breast cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

[0148] Because kinases plays an active role in angiogenesis certain compounds described herein are useful for modulating angiogenesis. Angiogenesis, the formation of new blood vessels from preexisting ones, plays a critical role in many pathological settings, including cancer, chronic inflammation, diabetic retinopathy and macular degeneration. Angiogenesis is regulated by multiple cell-signaling pathways, including pathways controlled by cellular kinases. Blocking angiogenesis, through the modulation of cell kinases, therefore, represents an effective approach to the treatment of diseases such as cancer. Thus methods of treatment include administering a sufficient amount of a compound or form thereof of the invention to decrease the symptoms or slow the progression of these diseases or disorders by inhibiting the rate of angiogenesis in a tissue.

Diseases and Disorders Responsive to Hsp90 Complex Modulation

[0149] Compounds described herein are useful for treating a patient suffering from a disease or disorder responsive to Hsp90 complex modulation

[0150] The Hsp90 complex or it substrate proteins have been implicated in a number of cancerous conditions. Thus Hsp90 complex inhibitors of the invention are particularly useful in the treatment of cancer, including, but not limited to, chronic myeloid leukemia, melanoma, breast, ovarian, brain, lung, thyroid, colorectal, prostate, and bladder cancer. Because of the role of Hsp90 in modulating the cellular stress response Hsp90 inhibitors of the invention are also useful in the treatment of heart disease, stroke, and neurodegenerative diseases including multiple sclerosis, Alzheimer's dementia, and ischemic optic neuropathy. Thus methods of treatment include administering a sufficient amount of a compound or form thereof of the invention to decrease the symptoms or slow the progression of these diseases or disorders.

Combination Therapy

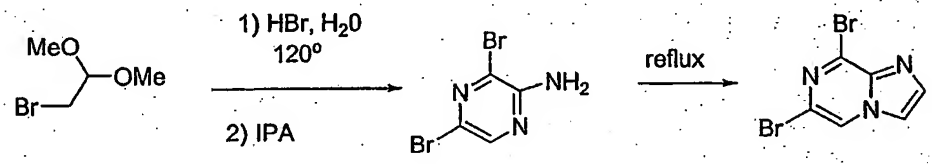
administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

EXAMPLES

[0155] The invention is illustrated by the following non-limiting examples. Exemplary syntheses of compounds of the Formula I are included in this section.

EXAMPLE 1. SYNTHESIS OF 1-(2-METHOXY-5-TRIFLUOROMETHYL-PHENYL)-3-{3-[8-(2-PYRIDIN-4-YL-IMIDAZOL-1-YL)-IMIDAZO[1,2-A]PYRAZIN-6-YL]-PHENYL}-UREA (Compound 6)

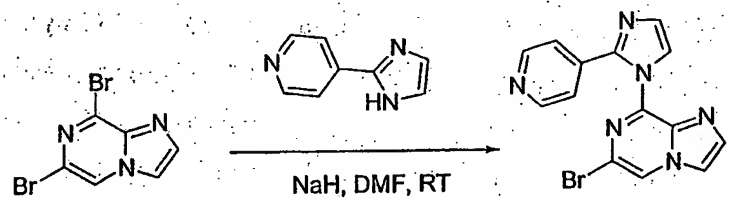
Step 1. Preparation of 6,8-dibromoimidazo[1,2-a]pyrazine (Compound 3)



1 2 3

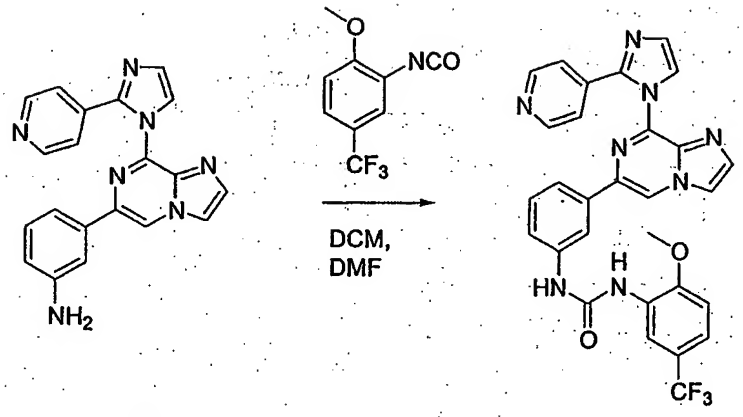
[0156] A mixture of bromoacetaldehyde dimethyl acetal (**1**) (51 grams (g)), 48% hydrobromic acid (HBr) (11 milliliters (ml)), and water (11 ml) is heated at 120 °C for 1 hour (hr). The solution is cooled, poured into a mixture of sodium bicarbonate ($NaHCO_3$) (60 g) and isopropyl alcohol (IPA) (200 ml), and stirred for 0.5 hr. The mixture is filtered, and the filtrate treated with 3,5-dibromo-2-aminopyrazine (**2**) (33 g) and heated under reflux for 16 hr. The suspension is cooled in ice, treated with 48%HBr (3 ml) and diethyl ether (60 ml) and filtered to give (**3**) (33 g) as the hydrobromide salt.

Step 2. Preparation of 6-Bromo-8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazine (Compound 4)



3 4

[0157] Sodium hydride (NaH) (730 milligrams (mg) of a 95% dispersion in mineral oil) is added to a solution of 4-(1*H*-Imidazol-2-yl)-pyridine (4.0 g) in N,N,-



5 6

[0159] A solution of 3-[6-Bromo-8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenylamine (5) (400 mg), 2-isocyanato-1-methoxy-4-trifluoromethyl-benzene (246 mg), in dichloromethane (DCM) (3 ml) and DMF (0.5 ml) is stirred at room temperature for 16 hr. The mixture is concentrated *in vacuo*, the residue slurried with diethyl ether/methanol (20:1), and filtered to give 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea (6) (468 mg) as a white solid.

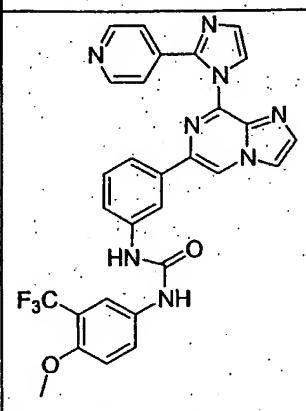
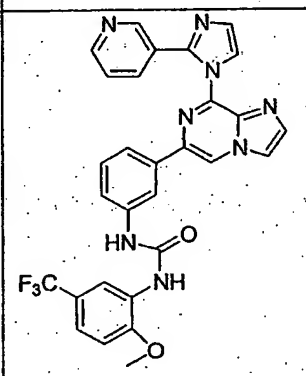
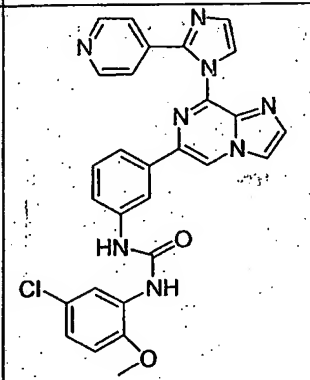
EXAMPLE 2. ADDITIONAL KINASE INHIBITORS

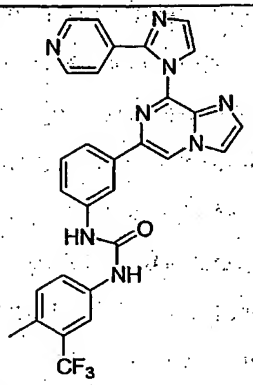
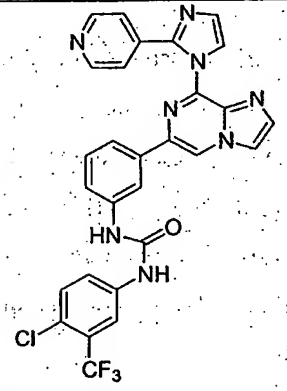
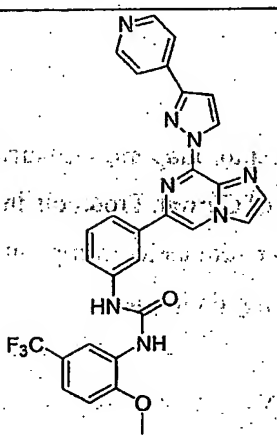
[0160] The following compounds are synthesized via the procedure set forth in Examples 1 and 2. In some instances changes in starting materials and reaction conditions that will be readily apparent to those skilled in the art of organic synthesis may be required.

[0161] LC-MS data reported in this example is obtained as follows:

LC conditions: RP-HPLC is performed on an AGILENT 1100 Binary HPLC system. The column is a Restek Ultra IBD 5 μm 1.0 x 30 mm (Cat. #: 9175331). The Mobile Phase contains component A, 0.2% Formic Acid/Water), and component B, Acetonitrile.

The following Gradient is used:

Cmp. #	Structure	Name	M + H	Ret. Tiime
8		1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	571.17	1.72
9		1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-3-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	571.19	1.90
10		1-(5-Chloro-2-methoxy-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	537.2	1.79

Cmp. #	Structure	Name	M + H	Ret. Tiime
14		1-(4-Methyl-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	555.21	1.81
15		1-(4-Chloro-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	575.16	1.84
16		1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(3-pyridin-4-yl-pyrazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea	571.19	1.74

EXAMPLE 3. PREPARATION OF RADIOLABELED PROBE COMPOUNDS OF THE INVENTION

[0163] The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a

dithiothreitol (DTT); 100 micromolar (μM) sodium vanadate; and 10 mM magnesium chloride ($MgCl_2$). The final reaction volume is 40 microliters (μl). The reaction mixture is incubated in a 96-well Pierce REACTI-BIND streptavidin-coated high binding capacity coated white plate (Pierce # 15502) coated with saturating amounts of biotinylated Crosstide peptide (UBI #12-385; biotin-KGSGSGRPRTSSFAEG; 50 picomoles (pmoles); about 1.25 μM) and initiated with the addition of 2.5 microcurie (μCi) ^{32}P-gamma-ATP (specific activity 3000 Ci/mmole; 10 mCi/ml; about 21 nanomolar (nM)). Compounds are initially tested in duplicate wells for determination of initial IC_{50} inhibition in half log serial dilutions starting at 100 uM with a final concentration of 2% dimethyl sulfoxide (DMSO). Following a 30 min. (minutes) incubation at 30°C, the reaction is stopped by aspiration tested 4 x 100 ul washes with TBS plus 0.05% Tween-20 prior to addition of 100 μl scintillant and counting in a Beckman TopCount instrument.

[0168] Percent inhibition is calculated as [1-((AVE CPM $_{compound}$ – AVE CPM$_{no\ peptide\ background}$)/(AVE CPM $_{no\ compound\ MAX}$ – AVE CPM $_{no\ peptide\ background}$)))*100]. Staurosporine, a general ATP competitive kinase inhibitor is used as a reference compound. Staurosporine exhibits an IC_{50} of approximately 60-100 nM for AKT-1 in the current assay format. Approximate S/N ratios are 8-12 X with AVE CPM of Maximum about 15k and no peptide background about 1.5 K. Improved S/N ratios can be obtained using higher amounts of either AKT-1 kinase or ^{32}P-gamma-ATP. Cold ATP is not added in current format but has been added at up to 200 μM in the presence of 5 μCi ^{32}P-γATP resulting in S/N ratios of approximately 5-10X.

EXAMPLE 6. SECOND AKT-1 KINASE ASSAY

[0169] Another standard AKT-1 Kinase Assay used to test compounds disclosed in this application may be performed as follows.

[0170] Materials include: 96-well isoplates (Perkin-Elmer Corp., Cat.# 1450-514) Biotinylated crosstide (Upstate Corp, Cat.#12-385), PKBα/AKT-1 (Panvera Corp., Cat# R3878), Adenosine 5'-triphosphate, [gamma-^{32}P] (Perkin Elmer Corp., Cat.# NEG302H001MC), and Streptavidin Coated Beads (Amersham Corp., Cat # RPNQ0007).

concentrations (in 25 ul) of 0.01% BSA, 1X Cell Signaling Kinase Buffer, 0.5 μM PTK Biotinylated Peptide Substrate 2, and 60 ng/well of $EphB_4$ kinase is added to all wells, except the four negative control wells (which contain no kinase), and mixed. To initiate the reaction, 5 μL of 550 uM ATP is added to each well. (Final Concentration of ATP = 110 μM). The reactions are incubated for 1 hour at room temperature (RT). After incubation a quantity of 8.35 μL of a 4X SA-APC Detection Mix is added to each well. The final concentration of Eu-labelled PT66 antibody is 1 nM and the SA-APC is 20 nM (based on the SA moiety). The reaction plates are incubated at RT for at least 15 minutes after SA-APC Detection Mix addition. The reaction plates are read on an Envision plate reader (Perkin-Elmer) with 605nm Excitation and 605nm and 640nm Emission wavelengths. Values are corrected for the fluorescence in the absence of enzyme and inhibition curves are fit to the data using a Logit curve-fitting algorithm. IC_{50} values are determined from these inhibition curves.

EXAMPLE 8. EPHB4 CELLULAR ASSAY

[0175] The following cell-based assay may also used to determine the effect of compounds on $EphB_4$ activity.

[0176] HEK293 cells stably expressing V5-epitope tagged $EphB_4$ are grown to ~75% confluency, and then incubated for 1 hr at 37 °C in low serum media (Optimem) containing test compound. Cells are stimulated for 10 minutes at 37 °C with 500ng/ml $EphrinB_2$/Fc chimera and 50ng/ml goat-anti-human IgG (FC specific) in low serum media containing test compound. Cells are washed in ice-cold PBS, lysed, and protein assays are performed on the cleared lysates. Equal protein amounts of each sample are subjected to SDS-PAGE and western blotting with either an anti-phosphotyrosine antibody or an anti-V5 antibody to control for total amounts of v5-tagged $EphB_4$ in each lysate.

[0177] Another generalized procedure for a standard cellular Kinase Assay used to test compounds disclosed in this application is as follows.

EXAMPLE 9. BIOCHEMICAL ASSAY

[0178] The following assay is a standard biochemical assay used to test activity of compounds as inhibitors of c-Kit, VEGF-R2, and Tie-2 kinase activity.

are analyzed for depletion of an HSP90 substrate protein, such as ErbB2 (Anti-ErbB2: Santa Cruz #SC-284), and increased levels of HSP70 (Anti-HSP70, Transduction Labs #610608). An antibody against a protein that is not an HSP90 client protein, such as PKA (Anti-PKA Transduction Labs #610980), is used as a loading control. Detection is via a horseradish peroxidase (HRP)-conjugated second antibody.

EXAMPLE 11. TUMOR CELL MONOLAYER PROLIFERATION ASSAY:

[0183] Test compounds are diluted to 1% DMSO, final concentration, and incubated with 3-5 x 10^3 tumor cells (for example MCF-7 or HCT-15 cells) in a final volume of 200 μl for 5 days. CELLTITER 96 AQUEOUS ONE Solution Cell Proliferation Assay (Promega, Madison WI), a colorimetric assay for determining the number of viable cells is used to quantitate cell growth. In this method, 10-20 μl MTS reagent is added to each well according to manufacturer's instructions, plates are incubated at 37°C and read at OD 490 nm. During the incubation period living cells covert the MTS reagent to a formazan product which absorbs at 490 nm. Thus the 490 nm absorbance is directly proportional to the number of living cells in culture.

[0184] For saturation binding analysis cell proliferation is response to a range of test compound concentrations is determined, for example 6 or 11 concentrations test compound concentrations, from 10 μM to 20nM may be used. Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values.

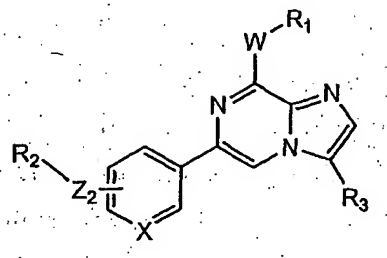
EXAMPLE 12. TEST RESULTS

[0185] Compounds 7 to 16 disclosed herein were tested in the assay of Example 7 and found to exhibit an IC_{50} of 10 micromolar or less. Certain compounds described herein exhibited an IC_{50} of 500 nanomolar or less, and certain particularly preferred compounds exhibited an IC_{50} of 100 nanomolar or less, in the assay of Example 7. Compounds 7 to 16 were also tested in the VEGF-R2 assay of Example 9 and found to exhibit and IC_{50} of less than 2 micromolar, certain preferred compounds among compounds 7 to 15 were found to exhibit an IC_{50} of less than 100 nanomolar in the VEGF-R2 assay of Example 9. Certain compounds 7 to 15 were tested in the c-Kit and Tie-2 assays of Example 9 and found to exhibit an IC_{50} of less than 500 nanomolar in the Tie-2 assay and less than 1 micromolar in the c-Kit assay. Certain preferred examples of compounds 7 to 15 were found to exhibit an IC_{50} of less than

CLAIMS

What is claimed is:

1. A compound having Formula 1:



(Formula 1)

and the pharmaceutically-acceptable salts and prodrugs thereof, wherein:

R_1 is pyridyl or pyrimidinyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, C_1-C_6alkylthio, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and –C(O)R_{13} where R_{13} is C_1-C_3haloalkyl, phenyl, heterocycloalkyl, or heteroaryl;

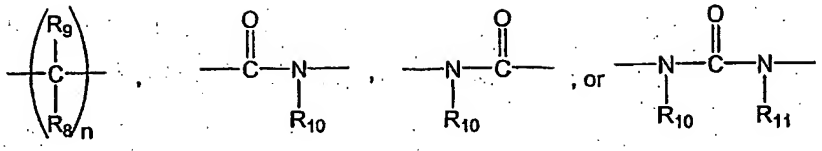
W is phenyl or a 5- or 6-membered heteroaryl containing from 1 to 4 heteroatoms independently chosen from nitrogen, oxygen, and sulfur; wherein W is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl;

X is N or CH;

R_2 is C_1-C_7alkyl, C_3-C_7cycloalkyl(C_0-C_2alkyl), heterocycloalkyl(C_0-C_2alkyl), C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, or (C_1-C_6alkoxy)C_1-C_6alkoxy; or

chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6 alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and –C(O)R_{13}; or

R_3 is phenoxy phenyl, each of which phenyl rings is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and –C(O)R_{13}.



wherein

R_8 and R_9 are independently hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, or halogen; and n is 0, 1, or 2;

R_{10} and R_{11} are independently

(iii) hydrogen or C_1-C_6alkyl; or

(iv) phenyl or a 5- or 6 membered heteroaryl ring, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl;

R_3 is hydrogen or C_1-C_6alkyl, or

R_3 is C_3-C_7cycloalkyl(C_0-C_2alkyl), heterocycloalkyl(C_0-C_2alkyl), phenyl, or a 5- or 6-membered heteroaryl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl; or

R_3 is phenoxyphenyl, each of which phenyl rings is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and

3. A compound or salt according to Claim 2 wherein

R_1 is 3-pyridyl or 4-pyridyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, and mono- and di-(C_1-C_4alkyl)amino.

4. A compound or salt according to Claim 3 wherein

R_1 is 3-pyridyl or 4-pyridyl, each of which is substituted with 0 to 2 substituents independently chosen from fluoro, chloro, bromo, C_1-C_2alkyl, and C_1-C_2alkoxy.

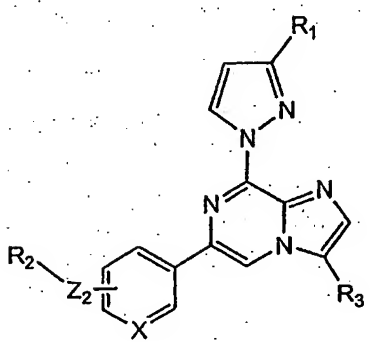
5. A compound or salt according to any one of Claims 1 to 4 wherein

W is phenyl, pyridyl, pyrimidinyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, sulfonamide, -CHO, halogen, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), and C_2-C_6alkanoyl

6. A compound or salt according to Claim 5 wherein

W is phenyl, pyridyl, pyrimidinyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, and mono- and di-(C_1-C_4alkyl)amino.

10. A compound or salt according to any one of Claims 1 to 4 of Formula 4

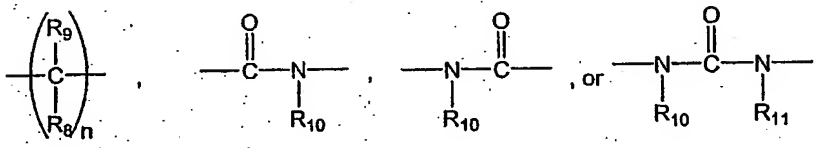


(Formula 4).

11. A compound or salt according to any one of Claims 1 to 10, wherein X is N.

12. A compound or salt according to any one of Claims 1 to 10, wherein X is CH.

13. A compound or salt according to any one of Claims 1 to 12 wherein Z_2 is



wherein

R_8 and R_9 are independently hydrogen or C_1-C_6alkyl; and n is 0, 1, or 2; and

R_{10} and R_{11} are independently hydrogen, C_1-C_6alkyl, or phenyl.

18. A compound or salt according to any one of Claims 1 to 17 wherein R_2 is phenyl, pyridyl, pyrimidinyl, pyrazinyl, imidazolyl, pyrrolyl, furanyl, thienyl, oxazolyl, or isoxazolyl, each of which may be either directly attached or bound via a C_1-C_2alkyl linker, and each of which is substituted with 0 to 3 substituents independently chosen from:

(i) hydroxy, halogen, nitro, cyano, amino, sulfonamide, -CHO, C_1-C_6haloalkyl, and C_1-C_6haloalkoxy, and

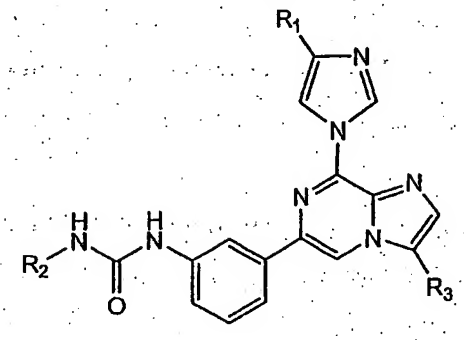
(ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, (C_1-C_6alkoxy)C_1-C_6alkoxy, C_1-C_6alkylthio, mono- and di-(C_1-C_6alkyl)amino, amino(C_1-C_6alkyl), mono- and di-(C_1-C_6alkyl)amino(C_1-C_6alkyl), C_2-C_6alkanoyl, and heterocycloalkyl(C_0-C_2alkyl); each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C_1-C_4alkoxy, C_3-C_7cycloalkyl, and mono- and di-(C_1-C_4alkyl)amino.

19. A compound or salt according to Claim 18, wherein R_2 is phenyl(C_0-C_2alkyl), pyridyl(C_0-C_2alkyl), or pyrimidinyl(C_0-C_2alkyl), each of which is substituted with 0 to 3 substituents independently chosen from:

(i) hydroxy, halogen, nitro, cyano, amino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and

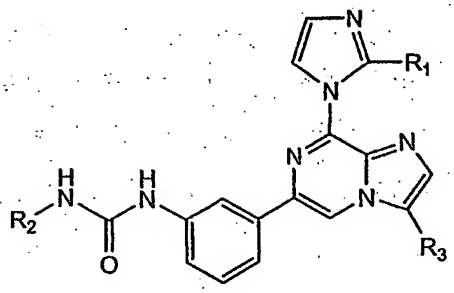
(ii) C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, (C_1-C_6alkoxy)C_1-C_6alkyl, C_1-C_4alkylthio, mono- and di-(C_1-C_4alkyl)amino, mono- and di-(C_1-C_4alkyl)amino(C_1-C_4alkyl), and heterocycloalkyl(C_0-C_2alkyl); each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C_1-C_4alkoxy, C_3-C_7cycloalkyl, and mono- and di-(C_1-C_4alkyl)amino.

24. A compound or salt according to Claim 1 of Formula 7



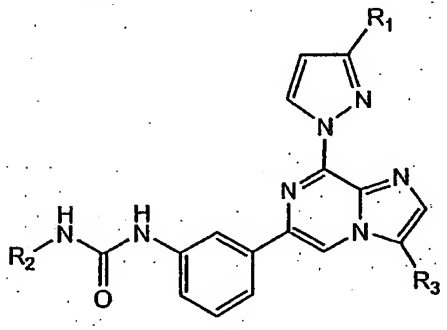
(Formula 7).

25. A compound or salt according to Claim 1 of Formula 8



(Formula 8).

26. A compound or salt according to Claim 1 of Formula 9



(Formula 9).

28. A compound or form thereof according to Claim 1, wherein the compound is:

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-3-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(5-Chloro-2-methoxy-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(5-Fluoro-2-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(5-Chloro-2-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(5-Chloro-2,4-dimethoxy-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(4-Methyl-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea;

1-(4-Chloro-3-trifluoromethyl-phenyl)-3-{3-[8-(2-pyridin-4-yl-imidazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea; or

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[8-(3-pyridin-4-yl-pyrazol-1-yl)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

29. A compound or form thereof according to any one of Claims 1 to 28, wherein the compound exhibits a IC_{50} of 1 micromolar or less in a standard in *vitro* assay of $EphB_4$ kinase activity.

30. A compound or form thereof according to any one of Claims 1 to 28, wherein the compound exhibits a IC_{50} of 500 nanomolar or less in a standard in *vitro* assay of $EphB_4$ kinase activity.

37. A method of reducing medication error and enhancing therapeutic compliance of a patient being treated for a disease or disorder responsive to tyrosine kinase activity modulation, the method comprising providing a packaged pharmaceutical preparation according to Claim 34 wherein the instructions additionally include contraindication and adverse reaction information pertaining to the package pharmaceutical composition.

38. A method of modulating $EphB_4$ kinase activity, the method comprising contacting cells expressing $EphB_4$ kinase with a compound or form thereof according to any one of Claims 1 to 28 in an amount sufficient to detectably inhibit $EphB_4$ kinase activity *in vitro*.

39. A method of modulating VEGF-R2 activity, the method comprising contacting cells expressing VEGF-R2 with a compound or form thereof according to any one of Claims 1 to 28 in an amount sufficient to detectably inhibit VEGF-R2 activity *in vitro*.

40. A method of modulating c-Kit activity, the method comprising contacting cells expressing c-Kit with a compound or form thereof according to any one of Claims 1 to 28 in an amount sufficient to detectably inhibit c-Kit activity *in vitro*.

41. A method of modulating Tie-2 activity, the method comprising contacting cells expressing Tie-2 with a compound or form thereof according to any one of Claims 1 to 28 in an amount sufficient to detectably inhibit Tie-2 activity *in vitro*.

51. The method of Claim 46 wherein the compound or form is administered orally.

52. A method for determining the presence or absence of an angiogenic kinase in a sample comprising contacting the sample with a compound or form thereof according to any one of Claims 1 to 28 under conditions that permit binding of the compound or form to the angiogenic kinase, detecting a level of the compound or form bound to the angiogenic kinase, and therefrom determining the presence or absence of the angiogenic kinase.

53. The method of Claim 52 wherein the angiogenic kinase is Tie-2, VEGF-R2, or $EphB_4$.

54. The method of Claim 53 wherein the compound or form thereof is radiolabelled.

55. The method of Claim 53, which additionally comprises separating unbound compound from bound compound; and determining the amount of bound compound in the sample.

56. The method of claim 42 wherein the cells expressing VEGF-R2, $EphB_4$, Tie-2, and c-Kit with a compound are contacted with the compound having a molecular weight less than 600 amu in an amount sufficient to detectably inhibit the activity of VEGF-R2, $EphB_4$, Tie-2, and c-Kit *in vitro*.

INTERNATIONAL SEARCH REPORT

tional Application No
T/US2004/003923

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DING ET AL: "A Combinatorial Scaffold Approach toward Kinase-Directed Heterocycle Libraries" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 124, no. 8, 2002, pages 1594-1596, XP002210160 ISSN: 0002-7863 the whole document	1-36

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 37 to 56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 29-31

Present claims 29 to 31 relate to a particular selection from a group of compounds defined by reference to a desirable characteristic or property, namely a certain IC50 value.

An attempt is made to further define the said group of compounds by reference to a result to be achieved.
This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as being described in claims 1 -28 as well as 32 to 56.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.